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Clinical outcomes of particle beam radiation therapy for patients with newly-diagnosed major salivary gland tumors

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Abstract

Background Major salivary gland tumors (MSGTs) are rare and pose significant treatment challenges. This study investigates the efficacy and safety of particle beam radiotherapy (PBRT) for patients with newly-diagnosed MSGTs.

Methods We conducted a retrospective analysis of 82 patients treated at the Shanghai Proton and Heavy Ion Center (SPHIC) between August 2015 and March 2022. The cohort received various radiotherapy regimens based on surgical history and pathological risk factors. We evaluated survival outcomes, treatment toxicity, and potential prognostic factors.

Results Our findings revealed promising 3-year survival rates: 94.3% for overall survival (OS), 81.3% for progression-free survival (PFS), 97.2% for locoregional control (LRC), and 82.6% for distant metastasis-free survival (DMFS). Acute and late toxicities were generally mild to moderate, with a favorable safety profile. Distant metastasis was the primary mode of treatment failure, emphasizing the need for early risk assessment.

Conclusion As a potentially safe and efficient treatment option for newly-diagnosed MSGTs, proton and carbon ion radiation offers an excellent alternative for traditional methods. More investigation is required to determine the long-term results and relative efficacy of various treatment modality for major salivary gland cancer when compared to photon therapy.

Keywords Proton, Carbon ion, Newly-diagnosed, Major salivary gland carcinoma, Initial clinical outcomes

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Introduction

Salivary gland carcinomas (SGCs), constituting a mere 5% of head and neck malignancies, represent an infrequent and complex oncological entity. These malignancies can be classified into major and minor salivary gland tumors based on their anatomical origin [1]. Among these, the sublingual, submandibular, and parotid glands have all exhibited the development of major salivary gland tumors (MSGTs), encompassing a diverse array of histologic subtypes and a wide spectrum of clinical behaviors [2, 3]. Significantly, the treatment sensitivity and prognosis of SGCs vary among distinct pathological types, including mucoepidermoid carcinoma, adenoid cystic carcinoma, and salivary duct carcinoma [4].

In the management of malignant tumors arising from the major salivary glands, surgical intervention has traditionally held a pivotal role. Nonetheless, radiation therapy, employed as an adjuvant therapy or as a radical curative modality, constitutes another critical therapeutic option [5]. For patients for whom surgery is infeasible, radical radiotherapy remains the sole recourse. Nevertheless, the effectiveness of conventional photon radiation in the context of salivary gland malignancies has displayed limitations, as borne out by prior research [6]. Particularly in cases characterized by high-risk pathological features, postoperative adjuvant radiation treatment has demonstrated its utility, improving survival rates by augmenting local control [7].

Particle radiotherapy (PBRT), encompassing proton and carbon ion therapy, offers a promising alternative. This approach delivers energy with a high degree of selectivity, thereby affording improved local control of the tumor, reduced risk of treatment-related toxicities, and minimized harm to adjacent normal tissues [8]. Notably, carbon ions, in particular, exhibit biological effects that may confer advantages, especially in cases resistant to conventional radiation [9]. The role of both photon and particle radiotherapy in the context of malignant SGCs, taking into account their differing biological and physical characteristics, has been subject to preliminary investigations. These investigations have suggested that PBRT may offer enhanced effectiveness with a diminished side effect profile when managing major salivary gland tumors [8, 10–16]. Despite the potential advantages of particle therapy elucidated in prior studies, there remains a paucity of clinical case studies assessing proton and carbon ion radiotherapy in the context of major salivary gland carcinomas, particularly with regard to the latter.

The primary objectives of the present study encompass a retrospective analysis of the clinical utility and initial therapeutic experience associated with particle irradiation in the treatment of newly-diagnosed malignant major salivary gland tumors at the Shanghai Proton and Heavy Ion Center (SPHIC). Furthermore, the study sought to evaluate patient survival outcomes, identify prognostic factors, and assess the incidence of treatment-related toxicity, thereby contributing valuable insights into the potential advantages of particle therapy in this specific clinical domain.

Methods

Patient and study

A retrospective study was conducted on the primary cohort of patients diagnosed with major salivary gland carcinoma at the Shanghai Proton and Heavy Ion Center (SPHIC), Shanghai, China, between August 2015 and March 2022. Inclusion criteria were as follows: patients receiving primary radiation therapy with adjuvant or curative intent, and histologically confirmed malignancy of the major salivary glands. Exclusion criteria included the presence of distant metastases at the initial diagnosis and tumor recurrence following radiation or surgery.

Treatment

Individualized treatment decisions for each enrolled patient were determined following multidisciplinary discussions at SPHIC, taking into account the patient's surgical history, current surgical condition, and other relevant factors. Patients with surgical contraindications or visible post-operative tumor remnants typically received radical radiation therapy. Adjuvant radiation was administered to patients with no residual tumor but exhibiting high-risk pathological factors, such as lymphovascular invasion (LVI) or perineural invasion (PNI). Detailed information on particle beam radiotherapy for the patients can be found in our previous studies [17, 18]. The evaluation of acute toxicities associated with PBRT was conducted using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.03). Additionally, late toxicities resulting from PBRT were analyzed using the Radiotherapy Oncology Group (RTOG) late radiation morbidity scoring system.

Statistical analysis

We assessed overall survival (OS), progression-free survival (PFS), locoregional control (LRC), and distant metastasis-free survival (DMFS) in our study. We employed the Kaplan-Meier method to determine survival rates and used the Cox proportional hazards analysis to identify independent predictors. Statistical analysis was performed using SPSS software (version 23.0, Chicago, IL, USA).

Results

Patient and tumor characteristics

In this retrospective analysis, we included a cohort of 82 consecutive patients newly diagnosed with major salivary gland carcinoma, who underwent PBRT treatment

between August 2015 and March 2022 at SPHIC. The median age of the patients was 38 years, ranging from 14 to 92 years. The most frequently affected salivary gland was the parotid gland, accounting for 59.8% of cases, followed by the submandibular gland at 34.1%. The predominant histological subtype was adenoid cystic carcinoma (ACC), which constituted 52.4% of cases, followed by mucoepidermoid carcinoma (14.6%) and adenocarcinoma (11.0%). Approximately 41.5% of patients underwent R2 excision or no surgical intervention, while the remaining 58.5% received R0 + R1 resection. A notable portion of the patients presented with advanced disease, with 35.4% having T3-4 tumors and 48.8% classified as stage III-IV.

The median biological effective dose (BED) of PBRT administered to the patients amounted to 85.1 Gy(RBE), with a range from 64.8 to 100.8. The median gross tumor volume for residual tumor was calculated at 32.02 ml, ranging from 1.74 to 194.29. All patients underwent radiotherapy using proton ($n = 17$), carbon ion ($n = 46$), or a combination of proton and carbon ion therapy ($n = 19$). Specifically, proton or carbon ion radiation was delivered to 48 patients who had undergone R0 or R1 resection. Meanwhile, among the 34 patients who had received R2 resection or had not undergone surgery, 13 received carbon ion radiation (70–72 Gy(RBE)/18–20 fractions), and 19 were treated with proton radiation (56 Gy(RBE)/28 fractions) followed by a carbon ion boost (15–18 Gy(RBE)/5–6 fractions). A typical treatment plan of mixed (A) IMPT plus (B) CIRT boost for parotid gland squamous cell carcinoma was shown in Fig. 1. A comprehensive overview of patient details and characteristics could be seen Table 1.

Treatment efficacy

For the entire patient cohort, the median follow-up duration was 38 months, ranging from 4 to 78 months. During this period, we observed one instance of locoregional failure, eleven cases of distant failures, and four patient deaths. Of these four deaths, three were attributed to the progression of metastatic lesions, while one was due to myocardial infarction. Distant metastases developed in eleven patients, including one case of teratocarcinosarcoma, two cases of adenocarcinoma, seven cases of adenoid cystic carcinoma, and one case of salivary duct carcinoma. Additionally, one patient with rhabdomyosarcoma experienced local recurrence following treatment.

In the overall cohort, the 3-year survival rates for overall survival (OS), progression-free survival (PFS), locoregional control (LRC), and distant metastasis-free survival (DMFS) were 94.3%, 81.3%, 97.2%, and 82.6%, respectively. These rates remained favorable at the 4-year mark, with OS, PFS, LRC, and DMFS rates of 92.1%, 81.3%, 97.2%, and 82.6%, as shown in Fig. 2. Among the 48 patients who received adjuvant particle beam radiotherapy (PBRT) following radical surgical resection (R0 + R1) due to pathological risk factors, the 3-year OS, PFS, LRC, and DMFS rates were 100%, 87.4%, 100%, and 87.4%, respectively.

Toxicity profile

The most commonly observed acute toxicities in our study were graded as 1–2 and included mucositis, dermatitis, and xerostomia. Some patients also reported grade 1–2 acute side effects such as hearing impairment, tinnitus, dysgeusia, and dysphagia. Notably, only one patient experienced a grade 3 acute mucositis response, and there were no cases of acute toxicities graded as 4 or 5.

In the context of late radiation side effects, the majority of cases were graded as 1–2, encompassing symptoms such as xerostomia, dysgeusia, and hearing impairment. Importantly, no cases of grade 3 or higher adverse responses were observed in the remaining patients. Acute and late side effects have been listed in Table 2.

Prognostic factors

To investigate potential prognostic factors for PFS and DMFS among various subgroups, we conducted both univariate and multivariate analyses. Survival probabilities were assessed using the log-rank test, considering factors such as age, gender, surgery status, primary site, pathology type, T and N category, clinical stage, RT type, BED, GTV, NLR, and PLR.

In the univariate analysis, we observed significant associations between PFS and surgery status ($P = 0.014$), T category ($P = 0.001$), and clinical stage ($P = 0.001$), all indicating worse PFS outcomes (Fig. 3). Subsequent multivariate analysis reaffirmed that T category ($P = 0.003$) was an independent prognostic factor affecting PFS (Table 3).

Furthermore, the univariate analysis revealed substantial correlations between DMFS and T category ($P = 0.001$), clinical stage ($P = 0.002$), and NLR ($P = 0.023$). Specifically, higher T category and clinical stage were associated with worse DMFS outcomes, while elevated NLR showed a potential impact (Fig. 4). In the multivariate analysis, T category emerged as an independent predictive factor for DMFS ($P = 0.003$). Although NLR displayed a tendency to influence DMFS, it did not reach statistical significance in the multivariate analysis ($P = 0.086$) (Table 4). These findings underscore the importance of T category as a robust prognostic indicator for both PFS and DMFS in our study.

Discussion

Major salivary gland tumors (MSGTs) are indeed a relatively rare form of tumor, and the utilization of proton and carbon ion radiation as a therapeutic modality is still in the developmental stage. In our retrospective analysis,

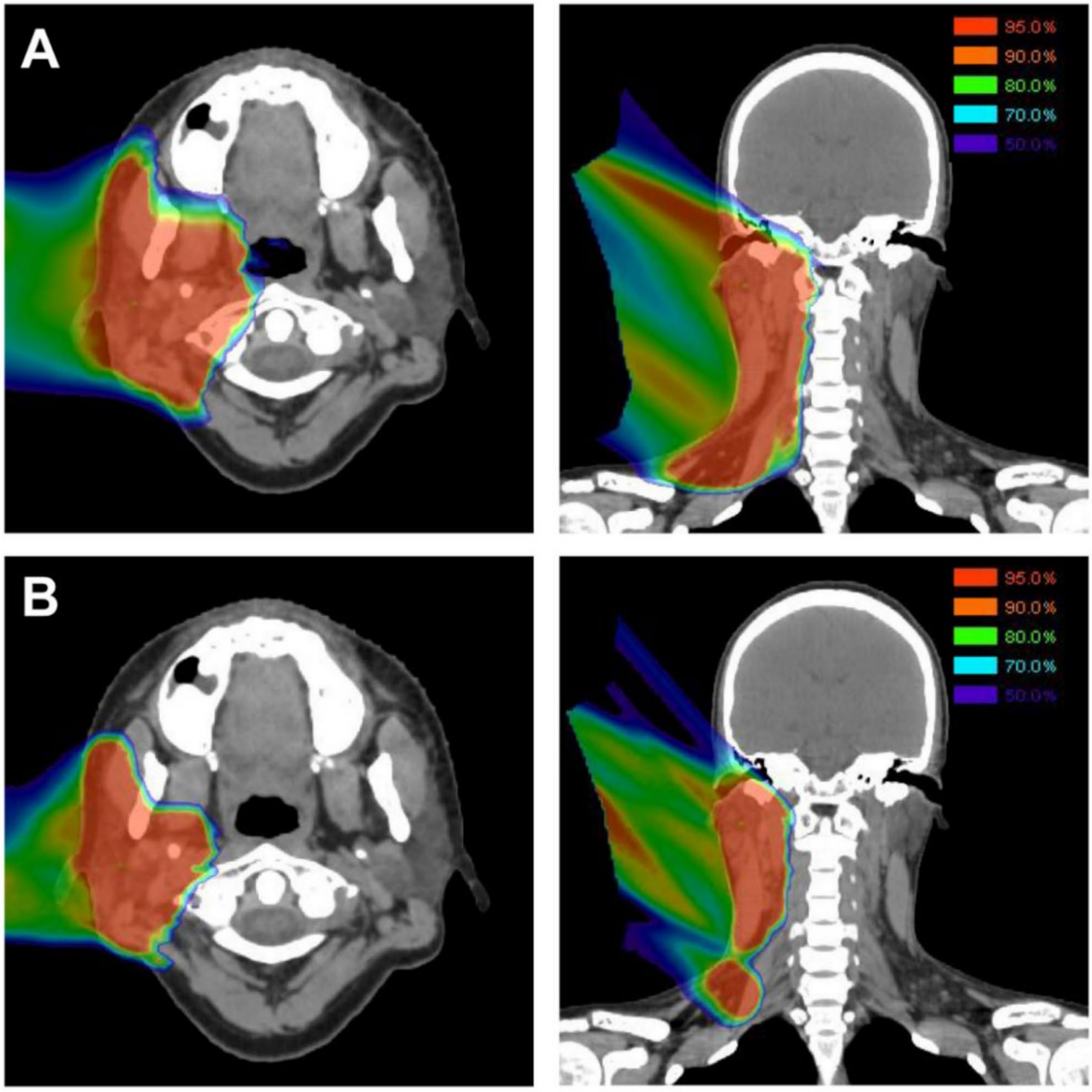

Fig. 1 A typical treatment plan of mixed (**A**) IMPT plus (**B**) CIRT boost for parotid gland squamous cell carcinoma. This was a patient with T2N2M0 disease treated with 56 Gy(RBE) of IMPT in 28 fractions plus 17.5 Gy(RBE) of CIRT in 5 fractions

we aimed to comprehensively assess the effectiveness and safety of PBRT in the treatment of 82 patients newly diagnosed with major salivary gland malignancies at SPHIC. The results of MSGTs after PBRT in published studies are listed in Table 5. Our analysis yielded promising results with 3-year survival rates of 94.3%, 81.3%, 97.2%, and 82.6% for OS, PFS, LRC, and DMFS, respectively. These findings highlight the excellent locoregional control achievable with PBRT in patients with newly diagnosed major salivary gland malignancies. Additionally, the mild to moderate adverse effects observed in our analysis further support the favorable safety profile of PBRT in this patient population.

The results obtained from our study underscore the favorable survival outcomes for patients subjected to PBRT, which are in line with previously reported research findings. Zakeri et al. conducted a study where they investigated clinical outcomes for Major Salivary Gland Tumors (MSGTs) treated with proton therapy. Their findings revealed remarkable 3-year rates of locoregional control and overall survival (OS) at 95.1% and 96.1%, respectively [10]. These results signify a notably

Table 1 Patients characteristics

Characteristic	No. of patients (%)
Median age (range)	38 (14–92)
Gender	
Male	41 (50%)
Female	41 (50%)
KPS	
90	51 (62.2%)
100	31 (37.8%)
Primary site	
Parotid gland	49 (59.8%)
Submandibular gland	28 (34.1%)
Sublingual gland	5 (6.1%)
Pathology	
Adenoid cystic carcinoma	43 (52.4%)
Adenocarcinoma	9 (11.0%)
Mucoepidermoid carcinoma	12 (14.6%)
Lymphoepithelial carcinoma	4 (4.9%)
Pleomorphic adenocarcinoma	2 (2.4%)
Squamous cell carcinoma	3 (3.7%)
Sarcoma	3 (3.7%)
Acinic cell carcinoma	2 (2.4%)
Salivary duct carcinoma	2 (2.4%)
Others	2 (2.4%)
Surgery status	
R0 + R1	48 (58.5%)
R2 + No surgery	34 (41.5%)
T category	
T1	13 (15.9%)
T2	40 (48.8%)
T3	14 (17.1%)
T4	15 (18.3%)
N category	
N0	65 (79.3%)
N1	12 (14.6%)
N2	4 (4.9%)
N3	1 (1.2%)
Clinical Stage	
I	12 (14.6%)
II	30 (36.6%)
III	20 (24.4%)
IV	20 (24.4%)
BED, Gy (RBE)	
Median/range	85.1 (64.8-100.8)
GTV, mL	
Median/range	32.02 (1.74-194.29)
NLR	1.96 ± 1.27
PLR	138.79 ± 47.62
Radiotherapy technique	
IMPT	17 (20.7%)
IMCT	46 (56.1%)
IMPT + IMCT	19 (23.2%)
IMPT	17 (20.7%)
66 Gy(RBE)/33Fx	4
63 Gy(RBE)/30Fx	1

Table 1 (continued)

Characteristic	No. of patients (%)
60 Gy(RBE)/30Fx	8
56 Gy(RBE)/28Fx	3
54 Gy(RBE)/27Fx	1
IMPT + IMCT	19 (23.2%)
56 Gy(RBE)/28Fx + 18 Gy(RBE)/6Fx	1
56 Gy(RBE)/28Fx + 17.5 Gy(RBE)/5Fx	12
56 Gy(RBE)/28Fx + 15 Gy(RBE)/5Fx	6
IMCT	46 (56.1%)
72 Gy(RBE)/18Fx	2
70 Gy(RBE)/20Fx	11
66.5 Gy(RBE)/19Fx	3
66 Gy(RBE)/22Fx	1
63 Gy(RBE)/18Fx	16
60 Gy(RBE)/20Fx	13

Abbreviations: BED: Biological effective dose; GTV: Gross tumor volume; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; IMPT: Intensity-modulated proton radiotherapy; IMCT: Intensity-modulated carbon-ion radiotherapy

high degree of local control within their specific study cohort. Similarly, Hanania et al. and Walser et al. presented data demonstrating the favorable local control achieved through proton therapy in patients with MSGTs [14, 15]. It is noteworthy that while some patients in these studies were not newly-diagnosed, the overall local control rate for the entire cohort remained notably satisfactory. This suggests that proton therapy holds substantial promise as an efficacious treatment modality for major salivary gland tumors. Moreover, carbon-ion therapy has also exhibited its potential to yield positive clinical outcomes in the management of major salivary gland tumors. In a study by Hayashi et al., they reported a 3-year local control rate of 81% and an overall survival rate of 94% for 69 cases of MSGTs following carbon ion radiotherapy [11]. However, it is pertinent to note that 17 of these cases were of patients who had experienced relapses, which might have had an impact on the local control results. Koto et al. documented the outcomes of radical carbon-ion radiotherapy for locally advanced parotid gland carcinomas, revealing 5-year local control (LC) and overall survival (OS) rates of 74.5% and 70.1%, respectively [12]. These findings underscore the significantly superior curative effect of carbon-ion radiotherapy compared to conventional photon radiotherapy. Notably, adenoid cystic carcinoma, a subtype generally considered to be radiation-resistant and constituting half of the cases in our study, exhibited a notably high rate of local control when treated with particle radiotherapy. In the study by Sulaiman et al., 289 patients with head and neck adenoid cystic carcinoma were treated with carbon-ion radiotherapy, yielding an impressive 2-year local control rate of 88% [19]. These results emphasize the advantage of carbon-ion therapy in managing this specific pathological subtype. In our prior research, which encompassed 55 patients with major salivary gland cancers, including both newly-diagnosed and recurrent cases, we observed a local recurrence-free survival (LRRFS) rate of 94.2% at 2 years following particle beam irradiation [17]. Given the paramount importance of these findings in managing this disease, the studies mentioned above collectively highlight the promising and beneficial role of proton and carbon-ion therapies in the treatment of major salivary gland malignancies.

In this study, the treatment modalities for the included patients encompassed three types of radiotherapy: proton, carbon ion, and proton combined with carbon ion boost. Postoperative patients received adjuvant proton or carbon-ion radiotherapy, while curative-intent patients underwent carbon ion or proton combined with carbon ion boost. Due to the limited number of cases related to particle beam radiotherapy for major salivary gland tumors in both prior studies and this research, there is a need to further expand the sample size. This expansion is essential for investigating which treatment modality, whether adjuvant or curative, offers superior efficacy and fewer side effects for malignant tumors of the major salivary glands. Concurrently, our center has also initiated prospective clinical studies to preliminarily explore these outcomes.

In addition to the observed improvement in local control with particle beam radiotherapy in the management of major salivary gland malignancies, our study highlighted that the primary mode of failure in the current research was distant metastasis. These results align with those of previous studies, emphasizing the high incidence of distant metastasis in major salivary gland malignancies. Preclinical studies have previously suggested that particle beam radiotherapy may have the potential to inhibit metastasis when compared to photon radiotherapy [20, 21]. However, due to the limited number of cases and other confounding factors, the clinical

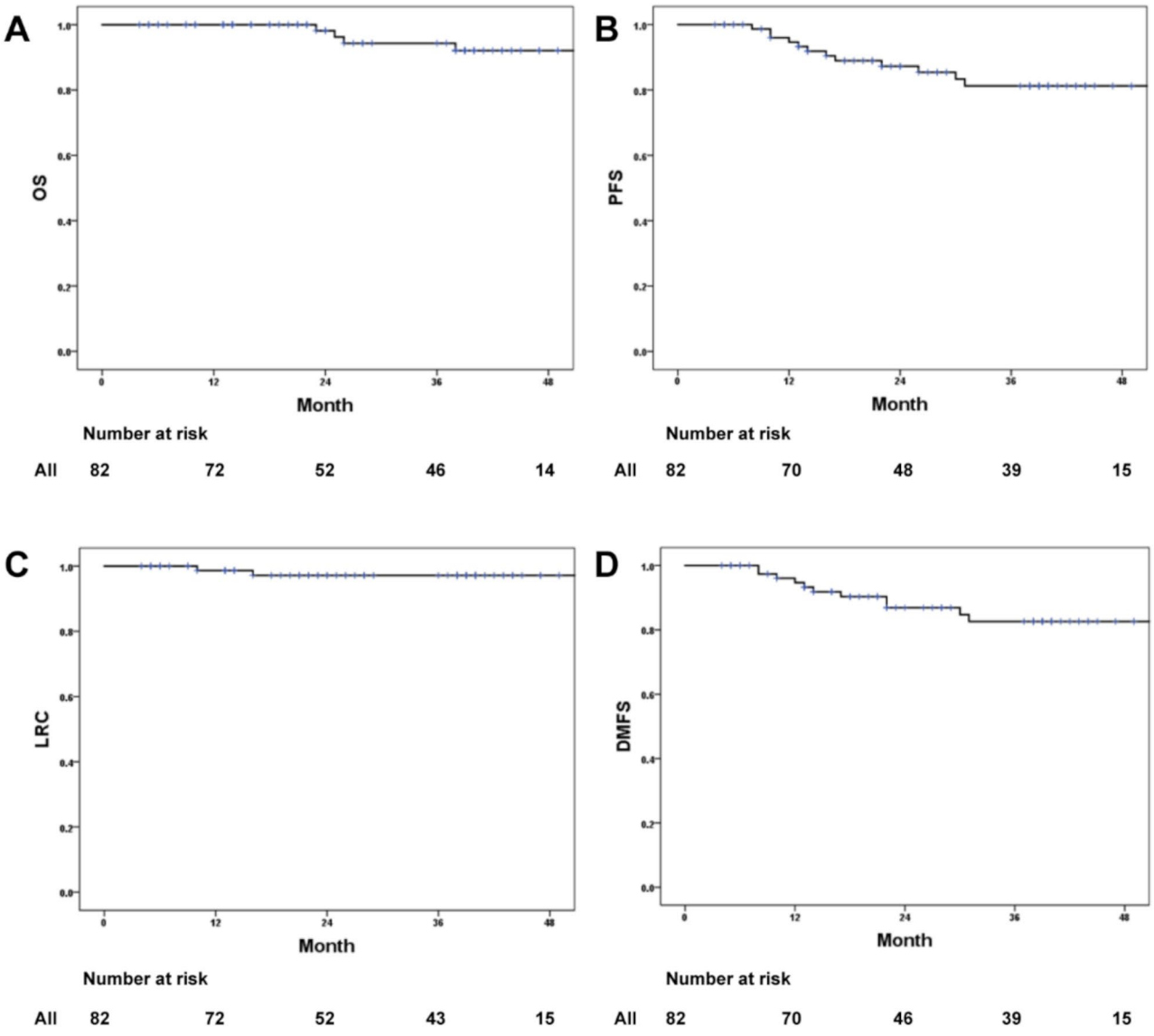

Fig. 2 Kaplan-Meier plots of (**A**) overall survival, (**B**) progression-free survival, (**C**) local-regional control, and (**D**) distant metastasis free survival

outcomes of this study may not fully reflect the potential advantage of particle therapy in reducing distant metastasis. If we could predict the risk of distant metastasis through specific indicators before initiating PBRT, we might intervene early to mitigate the risk, thereby maximizing the benefits of particle therapy for these patients. Two simple indices of interest that have arisen for cancer patient investigations are the pre-treatment platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR). Research from the past has demonstrated that elevated NLR or PLR is associated with a lower overall survival (OS) and a higher risk of distant metastases in a variety of cancer types, including major salivary gland tumors [22, 23]. The univariate analysis of this study revealed a strong correlation between NLR and DMFS, while the multivariate analysis revealed no statistical significance ($P = 0.086$). The limited number of instances may have contributed to this outcome. Therefore, more thorough models or widely used indicator could be required to confirm a patient's risk of distant metastases and to indicate the potential benefits of subsequent particle beam radiation therapy.

Investigating the potential of particle beam radiation for the treatment of major salivary gland cancers also involves assessing the potential for severe side effects. With the exception of one patient who had grade 3 acute oral mucositis, all of the study's individuals had grade 1–2 acute or late adverse effects, indicating that those who had major salivary gland tumors following particle radiation were well tolerated. Similar research' findings, which were previously highlighted, also point to mild or moderate toxicities from particle beam radiation

Table 2 Acute and late toxicities induced by PBRT

Toxicity	Grade, *n* (%)	
	Grade 1–2	Grade 3–5
Acute		
Mucositis	28 (24.3)	1 (1.0)
Dermatitis	58 (54.4)	0
Xerostomia	28 (31.1)	0
Hearing impairment	5 (6.8)	0
Tinnitus	4 (7.8)	0
Dysgeusia	2 (6.8)	0
Dysphagia	2 (1.9)	0
Late		
Xerostomia	19 (20.4)	0
Dysgeusia	7 (7.8)	0
Hearing impairment	7 (5.8)	0
Tinnitus	6 (8.7)	0
Dysphagia	4 (3.9)	0
Limited mouth opening	2 (1.9)	0
Mandibular osteomyelitis	1 (1.0)	0

[10–12, 15–17]. Following proton treatment, Chuong et al. documented the toxicities of one hundred and five MSGT patients. According to the findings, xerostomia (7.6%), nausea (1.5%), dysgeusia (4.8%), mucositis (10.5%), and dysphagia (10.5%) were among the acute grade 2 or higher toxicity symptoms [16]. Carbon ion-induced side effects are still mostly grade 1–2, with a very rare occurrence of grade 3 and beyond, even for parotid gland cancers following definitive radiation [12]. Moreover, prior dosimetry or side-effect comparison studies comparing photons and proton or carbon ions have verified that, when evaluating proton or carbon ion treatment plans, the dosage of exposure to neighboring normal tissues is greatly decreased [13, 14, 24–26]. It is proposed that this dosimetric advantage is clinically relevant for lowering acute toxicity when combined with the above dosimetry data and clinical side effect outcomes.

This study has several limitations. First, the relatively small sample size of 82 patients may limit the generalizability of our findings, and a larger cohort would provide more robust statistical power. Second, the lack of a direct comparison between PBRT and conventional photon

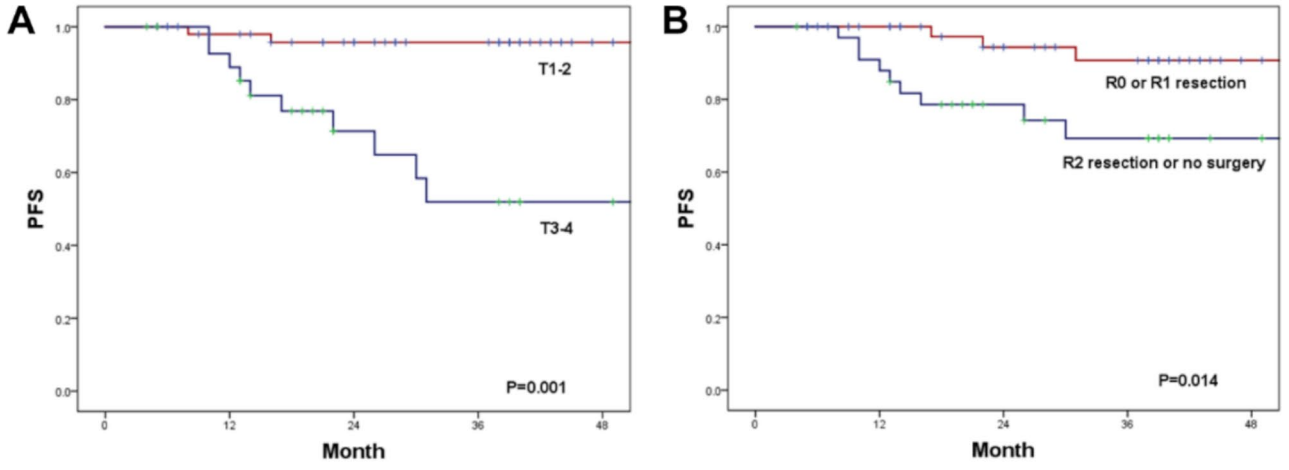

Fig. 3 Curves of progression-free survival stratified by T category (T1/2 versus T3/4) and surgery status (R0 + R1 vs. R2 + no suegery)

Table 3 Univariate and multivariate analysis for PFS

Characteristics		Univariate analysis	Multivariate analysis	
		p-value	HR (95.0% CI)	*p*-value
Age	≤ 38 vs. >38	0.562	-	-
Gender	Male vs. Female	0.266	1.43 (0.39–5.21)	0.591
Surgery status	R0-1 vs. R2 + no	**0.014**	0.54 (0.06–5.22)	0.594
Primary site	Parotid gland vs. Other	0.677	-	-
Pathology	ACC vs. Other	0.523	-	-
T category	T1-2 vs. T3-4	**0.001**	0.08 (0.02–0.43)	**0.003**
N category	N0 vs. N1-3	0.215	0.19 (0.03–1.16)	0.072
Clinical Stage	I-II vs. III-IV	**0.001**	-	-
BED	<85.1 vs. ≥85.1	0.140	0.72 (0.08–6.92)	0.779
GTV	<32.02 vs. ≥32.02	0.613	-	-
NLR	<1.96 vs. ≥1.96	0.188	0.83 (0.23-3.00)	0.770
PLR	<138.79 vs. ≥138.79	0.992	-	-

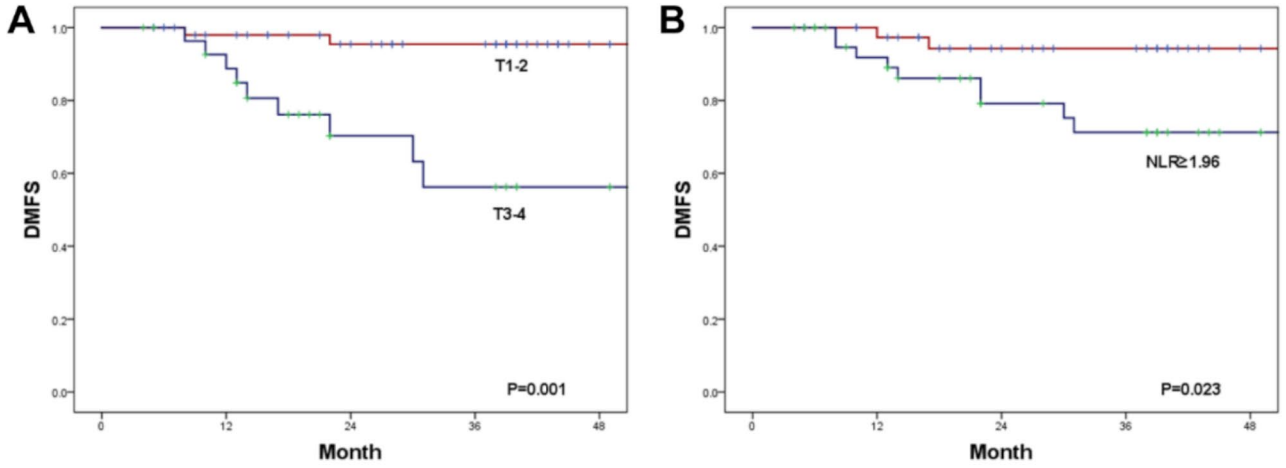

Fig. 4 Curves of distant metastasis free survival stratified by T category (T1/2 versus T3/4) and NLR status (NLR<1.96 vs. NLR ≥ 1.96)

Table 4 Univariate and multivariate analysis for DMFS

Characteristics		Univariate analysis	Multivariate analysis	
		p-value	HR (95.0% CI)	*p*-value
Age	≤ 38 vs. >38	0.123	3.03 (0.65–14.20)	0.160
Gender	Male vs. Female	0.137	0.286 (0.06–1.47)	0.134
Surgery status	R0-1 vs. R2 + no	0.096	0.83 (0.06–11.21)	0.887
Primary site	Parotid gland vs. Other	0.228	4.11 (0.95–17.79)	0.059
Pathology	ACC vs. Other	0.321	0.78 (0.14–4.49)	0.785
T category	T1-2 vs. T3-4	**0.001**	14.57 (2.46–86.42)	**0.003**
N category	N0 vs. N1-3	0.156	8.09 (0.87–75.43)	0.066
Clinical Stage	I-II vs. III-IV	**0.002**	-	-
BED	<85.1 vs. ≥85.1	0.171	2.74 (0.15–50.81)	0.499
GTV	<32.02 vs. ≥32.02	0.696	-	-
NLR	<1.96 vs. ≥1.96	**0.023**	6.11 (0.78–48.20)	0.086
PLR	<138.79 vs. ≥138.79	0.797	-	-

Table 5 Clinical outcomes of MSGTs following PBRT in previous published study

	RT type	Number of patient	Median follow-up time (m)	OS	PFS	LRC	DMFS
Koto (2015)	Carbon ion	46	62	5y OS 70.1%	5y PFS 49.2%	5y LC 74.5%	-
Hayashi (2018)	Carbon ion	69	32.7	3y OS 94% 5y OS 82%	3y PFS 51% 5y PFS 51%	3y LC 81% 5y LC 74%	- -
Adeberg (2019)	IMRT + Carbon ion boost	28	30	-	-	2y LC 96% 2y LRC 93%	-
Zakeri (2020)	Proton	68	36.4	3y OS 96.1%	3y PFS 80.7%	3y LRC 95.1%	3y DMFS 79.9%
Alexander (2021)	Proton	72	30	2y LC 89%	2y PFS 77%	2y LC 96%	-
Walser (2023)	Proton	26	46	4y OS 90%	-	4y LC 90% 4y LRC 87%	4y DC 77%
Current study	Proton Cabon ion	82	38	3y OS 94.3%	3y PFS 81.3%	3y LRC 97.2%	3y DMFS 82.6%

therapy makes it challenging to definitively determine the superiority of PBRT over standard treatment modalities. Prospective, randomized controlled trials are needed to address this. Third, while we observed promising outcomes in terms of local control, the high incidence of distant metastasis remains a significant concern, highlighting the need for further exploration into the potential role of systemic therapies in combination with PBRT. Lastly, our study primarily focused on short-term safety and efficacy, and longer follow-up is required to better

assess the late toxicities and long-term durability of treatment outcomes.

Conclusion

In conclusion, PBRT offer improved dose distribution, reduced toxicity, and potentially better clinical outcomes. Further research studies are needed to establish the comparative effectiveness compared to photon and long-term outcomes of these treatment modalities in major salivary gland carcinoma.

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Author contributions
Qingting Huang: design the study, collect data and analysis, interpretation, drafting, revising the article and final approval. Jiyi Hu: data collection, data analysis, revision and final approval. Weixu Hu: collect data, drafting, revision and approve of the version. Jing Gao: collect data, revision and approve of the version. Haojiong Zhang: collect patient's data, and approve of the version. Jiade Jay Lu: Conceptualization and design study, supervision, data analysis and results interpretation, revising the article, final approval. Lin Kong: Conceptualization and design study, supervision, data analysis and results interpretation, revising the article, funding acquisition, final approval.

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Data availability
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study has been granted an exemption form the requirement of written informed consent and human participants in this study were reviewed and approved by institutional review board (IRB) of Shanghai Proton and Heavy Ion Center (No. 230522EXP-01).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflicts of interest
The authors declare no conflicts of interest related to this study.

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